Systemic Anti-PD-1 Immunotherapy Results in PD-1 Blockade on T Cells in the Cerebrospinal Fluid.

Journal: JAMA Oncol

Publication Year: 2020

Authors: Jana Portnow, Dongrui Wang, M Suzette Blanchard, Vivi Tran, Darya Alizadeh, Renate Starr, Ramsinh Dodia, Vivian Chiu, Alfonso Brito, Julie Kilpatrick, Paige McNamara, Stephen J Forman, Behnam Badie, Timothy W Synold, Christine E Brown

PubMed link: 33030521

Funding Grants: Phase I Study of Chimeric Antigen Receptor Engineered Central Memory T cells for the Treatment of Malignant Glioma

Public Summary:
Importance Little is known about the penetration and bioactivity of systemically administered programmed cell death 1 (PD-1) antibodies in the central nervous system. Such information is critical for advancing checkpoint antibody therapies for treatment of brain tumors. Objective To evaluate pembrolizumab concentrations and PD-1 blockade on T cells in the cerebrospinal fluid (CSF) after intravenous administration. Design, Setting, and Participants Cerebrospinal fluid and blood samples were collected from 10 adult patients with high-grade gliomas who were participating in clinical trials of intracranially administered chimeric antigen receptor (CAR) T cells and intravenous pembrolizumab at City of Hope in Duarte, California, from 2017 through 2019. Neuropharmacokinetic and immunologic correlative studies were performed on CSF and serum samples. Interventions or Exposures Pembrolizumab, 200 mg, was given intravenously every 3 weeks with a median of 2 cycles (range, 1-8). CAR T cells were administered intracranially every 1 to 4 weeks. Cerebrospinal fluid and blood samples were collected on the day of CAR T-cell administration and then 24 hours later for a total of 100 paired samples. Main Outcomes and Measures Pembrolizumab concentrations were measured by enzyme-linked immunosorbent assay, PD-1 blocking on T cells by flow cytometry, and results of PD-1 blockade on CAR T-cell function by in vitro tumor rechallenge assays. Results Of the 10 patients included in this study, the mean (SD) age was 45.7 (11.0) years, and 6 (60%) were women. Steady-state pembrolizumab concentrations in the CSF were achieved by 24 hours after initial intravenous administration, with a mean CSF:serum ratio of 0.009 (95% CI, 0.004-0.014). The CSF concentrations of pembrolizumab effectively blocked PD-1 on both endogenous T cells and intracranially administered CAR T cells in the CSF, with flow cytometric detection of surface PD-1 on the T cells decreasing from a mean (SD) of 39.3% (20.2%) before pembrolizumab to a mean (SD) of 3.8% (5.8%) 24 hours after pembrolizumab infusion. Steady-state concentrations in the CSF were maintained throughout the 21-day cycle of pembrolizumab, as was the PD-1 blocking effect, evidenced by no increase in detectable surface PD-1 on T cells in the CSF during that time period. Incubation of PD-1–expressing T cells with CSF samples from patients treated with pembrolizumab also resulted in PD-1 blockade. Conclusions and Relevance Results of this study demonstrate steady-state concentrations of pembrolizumab in CSF after intravenous administration as well as CSF concentrations that are sufficient for blocking PD-1 on endogenous and adoptively transferred T cells. This provides mechanistic insight regarding the ability of systemically administered PD-1 blocking antibodies to modulate T-cell activity in the brain.

Scientific Abstract:
Importance: Little is known about the penetration and bioactivity of systemically administered programmed cell death 1 (PD-1) antibodies in the central nervous system. Such information is critical for advancing checkpoint antibody therapies for treatment of brain tumors. Objective: To evaluate pembrolizumab concentrations and PD-1 blockade on T cells in the cerebrospinal fluid (CSF) after intravenous administration. Design, Setting, and Participants: Cerebrospinal fluid and blood samples were collected from 10 adult patients with high-grade gliomas who were participating in clinical trials of intracranially administered chimeric antigen receptor (CAR) T cells and intravenous pembrolizumab at City of Hope in Duarte, California, from 2017 through 2019. Neuropharmacokinetic and immunologic correlative studies were performed on CSF and serum samples. Interventions or Exposures: Pembrolizumab, 200 mg, was given intravenously every 3 weeks with a median of 2 cycles (range, 1-8). CAR T cells were administered intracranially every 1 to 4 weeks. Cerebrospinal fluid and blood samples were collected on the day of CAR T-cell administration and then 24 hours later for a total of 100 paired samples. Main Outcomes and Measures: Pembrolizumab concentrations were measured by enzyme-linked immunosorbent assay, PD-1 blocking on T cells by flow cytometry, and results of PD-1 blockade on CAR T-cell function by in vitro tumor rechallenge assays. Results: Of the 10 patients included in this study, the mean (SD) age was 45.7 (11.0) years, and 6 (60%) were women. Steady-state

pembrolizumab concentrations in the CSF were achieved by 24 hours after initial intravenous administration, with a mean CSF:serum ratio of 0.009 (95% CI, 0.004-0.014). The CSF concentrations of pembrolizumab effectively blocked PD-1 on both endogenous T cells and intracranially administered CAR T cells in the CSF, with flow cytometric detection of surface PD-1 on the T cells decreasing from a mean (SD) of 39.3% (20.2%) before pembrolizumab to a mean (SD) of 3.8% (5.8%) 24 hours after pembrolizumab infusion. Steady-state concentrations in the CSF were maintained throughout the 21-day cycle of pembrolizumab, as was the PD-1 blocking effect, evidenced by no increase in detectable surface PD-1 on T cells in the CSF during that time period. Incubation of PD-1-expressing T cells with CSF samples from patients treated with pembrolizumab also resulted in PD-1 blockade. Conclusions and Relevance: Results of this study demonstrate steady-state concentrations of pembrolizumab in CSF after intravenous administration as well as CSF concentrations that are sufficient for blocking PD-1 on endogenous and adoptively transferred T cells. This provides mechanistic insight regarding the ability of systemically administered PD-1 blocking antibodies to modulate T-cell activity in the brain.

Source URL: https://www.cirm.ca.gov/about-cirm/publications/systemic-anti-pd-1-immunotherapy-results-pd-1-blockade-t-cells-cerebrospinal